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EMPIRICAL
Improving Treatment for Pneumonia in HIV-infected Infants

EMPIRICAL PROJECT

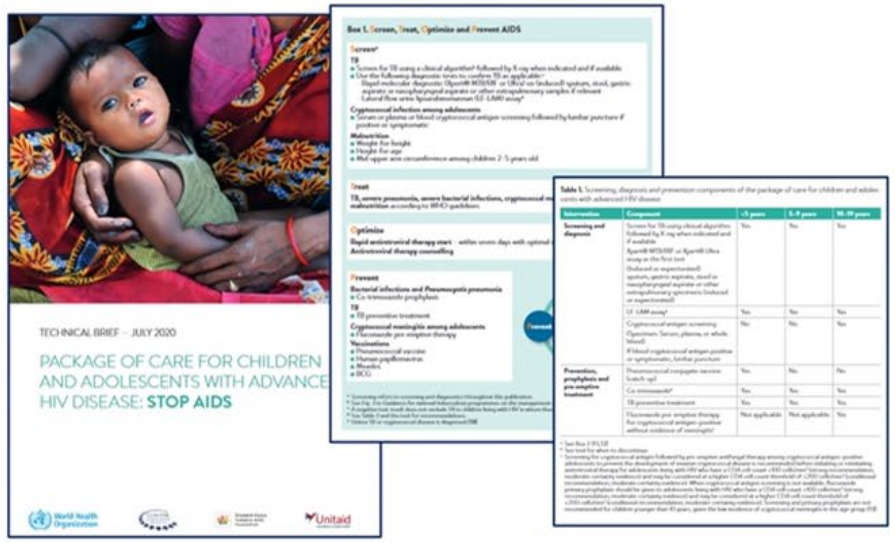
EDCTP

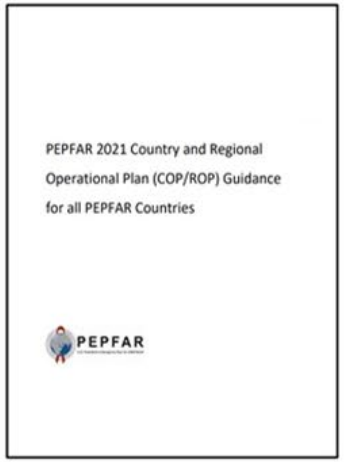
This project is part of the EDCTP2 programme supported by the European Union

In response to limited focus globally on Pediatric AHD, in 2020 the World Health Organization (WHO) released the STOP AIDS package of care for children and adolescents with AHD

- In July 2020, the WHO released a technical brief on a package of care for children and adolescents with advanced disease to lay a groundwork for proper care for young people living with AIDS

- PEPFAR's 2021 COP Guidance stated the need to incorporate this (2020 WHO STOP AIDS) package of AHD interventions into pediatric HIV programs
- Global Fund's Information Note (July 2022) identified the provision of a package of care that reduces mortality in individuals with advanced HIV disease in adults and children as a priority intervention





The guidance is now in place from WHO, donors and partners to enable countries to adopt, implement and scale up interventions to reduce AHD related mortality in children and adolescents

Ana Moore

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- **Empirical use of valganciclovir and tuberculosis treatment in chest indrawing and severe pneumonia in HIV-infected infants: a randomized controlled clinical trial**

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Clinical trials to reduce health inequities in pregnant women, newborns and children

Status:	Closed
Type of action:	Research and Innovation Action (RIA)
Call budget:	€38.23 M
Funding level:	Up to 100% of eligible costs
Stage 1 Open date:	4 July 2017, 17:00
Stage 1 Close date:	13 October 2017, 17:00
Stage 2 Open date:	22 December 2017, 17:00
Stage 2 Close date:	14 March 2018, 17:00

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Expected number of grants: 5-10
Call identifier: RIA2017MC

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Hypothesis

- Empirical treatment with valganciclovir and treatment against TB will improve survival in HIV infected infants with severe pneumonia.

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Primary Aims

1.1. To compare empirical treatment against CMV with valganciclovir (powder for solution, 50 mg/mL) versus no treatment

valganciclovir will reduce 15-day mortality

1.2. To compare empirical treatment against TB versus no treatment

TB treatment will reduce 1-year mortality

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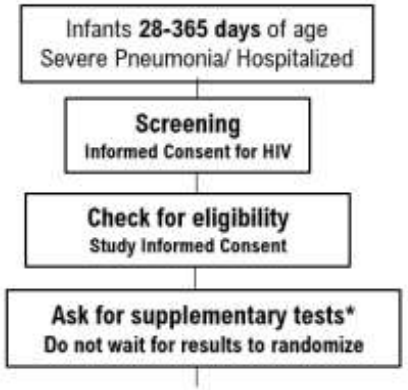

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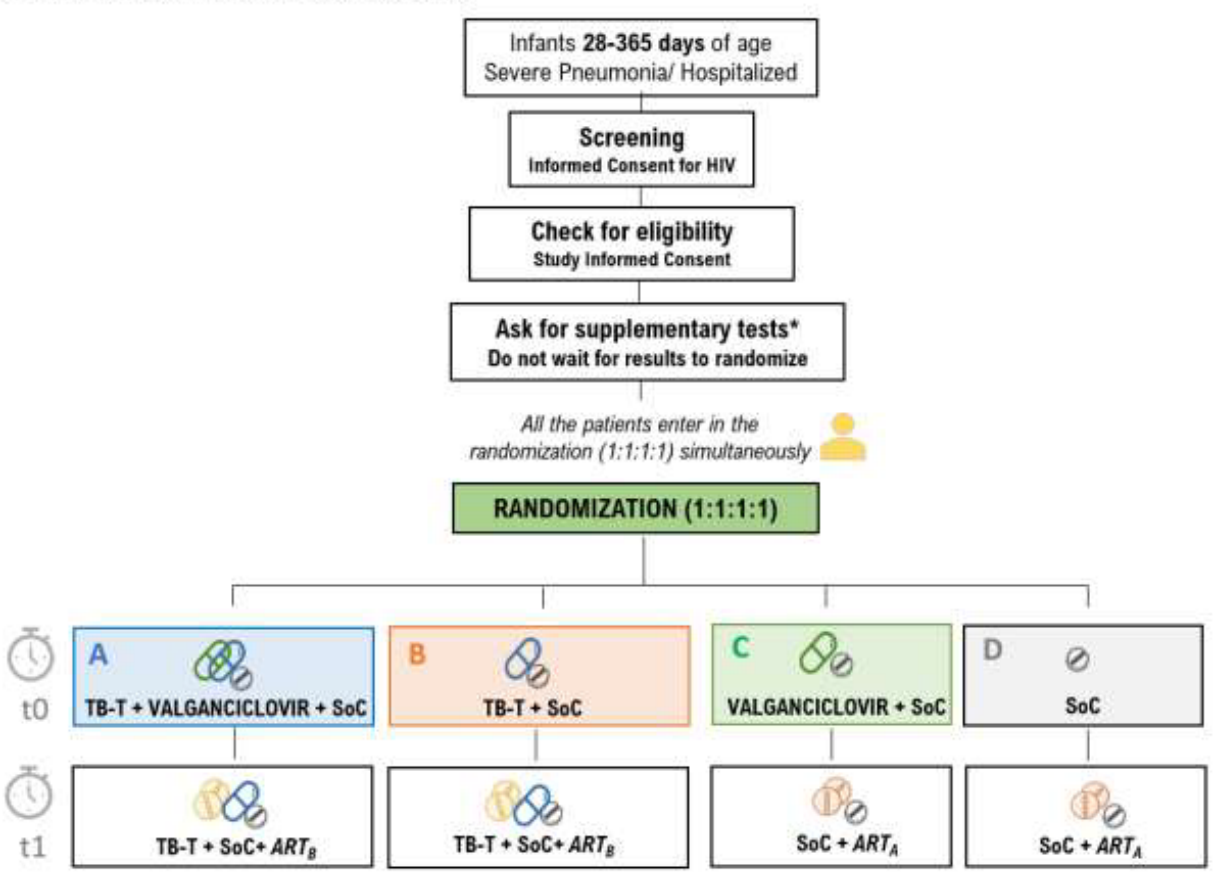

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- Phase II-III, open label, factorial trial
- 6 countries, 20 hospitals.
- Population:
  - 30 d-365 d
  - HIV+
  - Severe pneumonia
- Recruited **518**/600 children expected
- Finish recruitment January 31st 2024

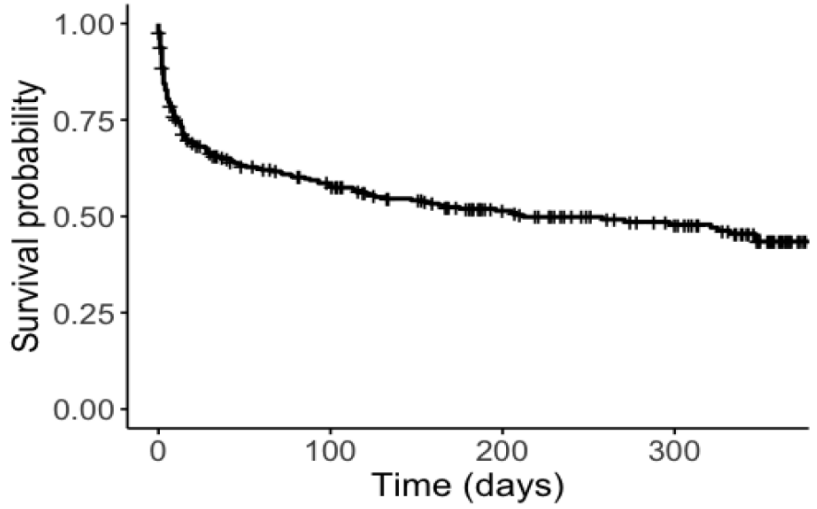
High Mortality in African Infants Hospitalized with Severe Pneumonia and Advanced HIV #810

Alfeu Passanduca[1], W. Chris Buck[1,2*], Alfredo Tagarro[3], Victor Musiime[4], Hilda Angela Mujuru[5], Chishala Chabala[6], Lola Madrid[3], Sara Domínguez-Rodríguez[3], Pui-Ying Iroh Tam[7], Tisungane Mvalo[6], Justina Magalhaes-Bramugy[9], Raoul Moh[10], Álvaro Ballesteros[3], Cinta Moraleda[7], Pablo Rojo[7], EMPIRICAL Clinical Trial Group

Table 1: Baseline patient characteristics

	n = 310
Demographic	
Age (months, median)	4.5 (IQR, 3.2-7.3)
Sex (female)	50%
Clinical	
Chest indrawing	284 (92%)
Oxygen saturation <90%	199 (64%)
Lethargic or unconscious	80 (26%)
Unable to drink/breastfeed	97 (32%)
Severe malnutrition	226 (73%)
Laboratory	
HIV viral load (median)	6.3 logs cp/mL (IQR, 5.8-7.0)
CD4% (median)	14.4% (IQR, 9.9-21.6)
White blood cell count (median)	12.9 (IQR, 8.7-18.7)
Hemoglobin (median)	9.2 (IQR, 8.1-10.2)
ALT (median)	21 (IQR, 14-37)

Figure 3: Kaplan-Meier survival analysis



The probability of 15-day and 12-month survival was 71% and 50%, respectively

Pasanduca A, CROI 2023

Adequate DTG exposure in infants on rifampicin treatment receiving twice-daily DTG

Tom G. Jacobs[1], Vivian Mumbiro[2], Uneisse Cassia[3], Damalie Nalwanga[4], Kevin Zimba[5], Sara Domínguez-Rodríguez[6], Constantine Mutata[2], W. Chris Buck[7], Chishala Chabala[5], Victor Musiime[4], Mutsa Bwakura-Dangarembizi[2], Cinta Moraleda[6], David M. Burger[1], Pablo Rojo[6], Angela Colbers[1], on behalf of the EMPIRICAL clinical trial group

[1]Radboud University Medical Center, Nijmegen, The Netherlands, [2]University of Zimbabwe Clinical Research Centre, Harare, Zimbabwe, [3]Universidade Eduardo Mondlane, Maputo, Mozambique, [4]Makerere University, Kampala, Uganda, [5]University Teaching Hospital, Lusaka, Zambia, [6]Fundación para la Investigación Biomédica del Hospital Universitario 12 de Octubre (imas12), Madrid, Spain, [7]University of California Los Angeles, Maputo, Mozambique

Demographics		Control arm (n=6)	Rifampicin arm (n=21)
Male/Female		3/3	13/8
Weight (kg)		5.9 (5.8-8.0)	6.4 (4.9-7.1)
Weight -band	*3-6kg*	2	11
	6-10kg	4	10
Age (months)		7.4 (6.4-8.8)	6.6 (5.6-10.5)
DTG dose mg/kg		1.86 (1.09-2.36)	1.33 (1.00-2.08)
Reported: Median(IQR)			

PK parameter	Control arm (n=6)	Rifampicin arm (n=21)	Geometric mean ratio
C_{trough} (mg/L)	1.11 (46)	1.05 (82)	1.05 (90% CI 0.69 - 1.60)
$AUC_{0\text{-}12h}$ (h*mg/L)	54.4 (39)	49.7 (70)	1.09 (90% CI 0.76 - 1.57)
C_{max} (mg/L)	3.86 (38)	3.36 (65)	1.15 (90% CI 0.81 - 1.63)
Reported: Geometric mean (CV%)			

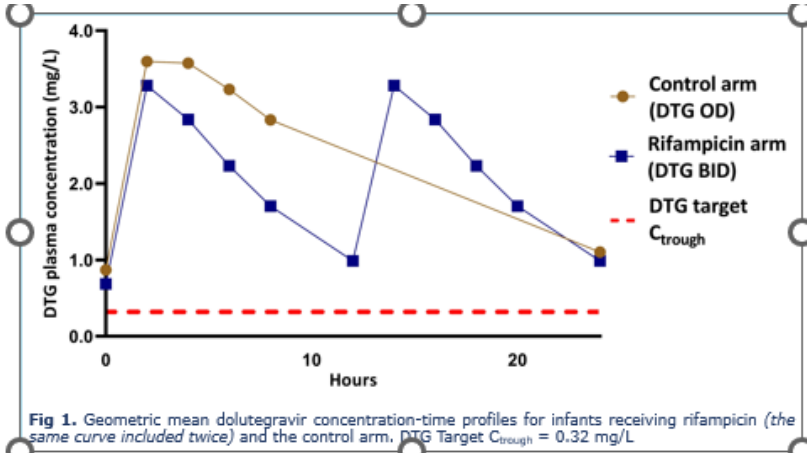


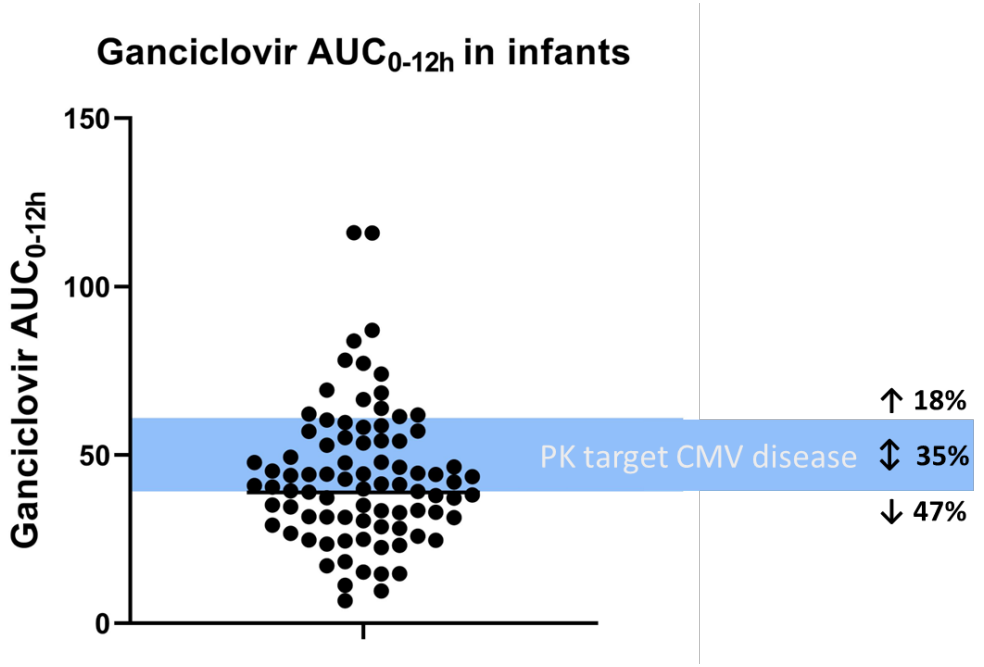
Fig 1. Geometric mean dolutegravir concentration-time profiles for infants receiving rifampicin *(the same curve included twice)* and the control arm. DTG Target C_{trough} = 0.32 mg/L

Jacobs T, Clin Infect Dis 2023 (accepted)

PK3, VALGANCICLOVIR LEVELS

- Valganciclovir reconstituted syrup was given at 16mg/kg/dose every 12 hours, and pharmacokinetic sampling was done 2 and 5 hours post-administration on day 3 of enrolment after at least 3 doses.

- The geometric mean AUC and proportion of subjects within the pharmacokinetic target for CMV treatment ($AUC_{0\text{-}12h}$ 40-60 h*mg/L) were determined.



Mumbiro V. IAS 2023

THANKS!